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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/865,018	05/24/2001	Joan Massague	GPCI-P08-079	4669

28120 7590 09/12/2003

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 09/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,018	MASSAGUE ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *1-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of group VI, claims 32-35 and added claims 36-47, in Paper No. 17 is acknowledged. The traversal is on the ground(s) that the species subjected election are encompassed by Markush groups and search for those species do not require serious burden, and normally ten sequences constitute a reasonable number for examination. This is not found persuasive because of the reasons or record. SEQ ID Nos. 2, 4 and 6 represent different and distinct polypeptide sequences encoded by DNA sequences derived from different genes. The chemical structures, physical properties and biological functions of different genes and their gene product differ from each other. Thus, SEQ ID Nos. 2, 4, and 6 are patentably distinct from each other and require separate search. This is not an election of species, rather this is an election from distinct inventions.

2. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-31 and SEQ ID Nos. 4 and 6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 17.

Claims 23, 25, 26, 32 and 33 have been amended. Claims 36-47 have been added. Claims 1-47 are pending, and claims 32-47 and SEQ ID No. 2 are under consideration.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The filing date of Application No. 08/275,983 is 7-15-94 **not 9-13-94**.

Claim Objections

5. Claims 36, 37, 42 and 43 are objected to because of the following informalities: SEQ ID Nos. 4 and 6 are non-elected inventions and will not be examined in the present Official action. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 38, 39, 44 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "composition of any of claims 32 and 36-37" in claims 38 and 39 is vague and renders the claims indefinite. A multiple dependent claim should refer back in the alternative to more than one preceding independent or dependent claim. Changing the phrase

"composition of any of claims 32 and 36-37" to "composition as in claims 32, 36 or 37" would be remedial.

The phrase "composition of any of claims 33 and 42-43" in claims 44 and 45 is vague and renders the claims indefinite. A multiple dependent claim should refer back in the alternative to more than one preceding independent or dependent claim. Changing the phrase "composition of any of claims 33 and 42-43" to "composition as in claims 33, 42 or 43" would be remedial.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 32-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 32-47 are directed to a pharmaceutical composition comprising a recombinant virus comprising a nucleic acid encoding a polypeptide having a sequence at least 90% identical to amino acid residues 28-88 of SEQ ID No. 2 and capable of inhibiting a cyclin E-Cdk2 complex, and a method for treating a subject, such as a human, suffering from hyperproliferative disorder, such as cancer, associated with a p27 protein mutation comprising administering to the subject said pharmaceutical composition. Claims 39 and 45 specify the recombinant virus is

papilloma virus, adenovirus, vaccinia virus, retrovirus, baculovirus, polyoma virus, Semliki virus, or SV40 virus.

The specification discloses nucleic acid sequence of human, mouse and mink kip1 cDNA sequences and shows kip1 protein binds to cyclin E-Cdk2 complex and inhibits Thr^{160} phosphorylation and activation of Cdk2. Transfection of Mv1Lu cells with expression vector expressing mouse kip1 protein and overexpression of said kip1 protein in said cells inhibits cell entry into S phase. The specification discloses that kip1 (28-79) inhibits Rb phosphorylation by cyclin A-Cdk2 with similar activity as full length kip1 and inhibits cyclin E-Cdk2 complex less effectively. Kip1 (28-79) missing 3 amino acids at N-terminal or 15 amino acids at the C-terminal are much weaker as Cdk inhibitors, and deletion of 7 N-terminal amino acids results in no inhibitory activity on Cdk (specification, p. 67-69).

The phrase "pharmaceutical composition" implies therapeutic effects in vivo. Claims 32-47 read on gene therapy in vivo. The claims encompass using any recombinant virus expressing a polypeptide comprising a sequence at least 90% identical to amino acid residues 28-88 of SEQ ID No. 2 for treating a subject having a hyperproliferative disorder associated with a p27 protein mutation.

The specification fails to provide adequate guidance and evidence for how to use a recombinant virus containing a nucleotide sequence encoding a plypeptide sequence having at least 90% identity to amino acid residues 28-88 of SEQ ID No. 2 for treating a subject having a hyperproliferative disease or disorder associated with a p27 protein mutation via various administration routes so as to provide therapeutic effect for said hyperproliferative disease in vivo.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reports that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus, far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (see page 239, right column). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3) and random integration of retroviral vector DNA into the host chromosome can lead to activation of unwanted genes or inactivation of transgenes (page 240, right column).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels

and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).

The specification discloses that kip1 (28-79) inhibits Rb phosphorylation by cyclin A-Cdk2 with similar activity as full length kip1 and inhibits cyclin E-Cdk2 complex **less effectively**. The kip1 peptide consists of amino acid residues 28-88 of SEQ ID No. 2 could have less inhibitory activity on Cdk as compared to SEQ ID No. 2 (human kip1 protein). The specification fails to provide adequate guidance and evidence that whether administering a recombinant virus expressing a peptide consists of amino acid residues 28-88 of SEQ ID NO. 2 via various administration routes would provide sufficient inhibitory effect on Cdk activity for treating hyperproliferative disease or disorder associated with a p27 protein mutation in vivo. In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use various recombinant virus containing a nucleotide sequence encoding a plypeptide sequence having at least 90% identity to amino acid residues 28-88 of SEQ ID No. 2 for treating a subject having a hyperproliferative disease or disorder associated with a p27 protein mutation via various administration routes so as to provide therapeutic effect for said hyperproliferative disease in vivo.

Further, the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for

different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2).

The claims read on deleting or adding amino acid residues within residues 28-88 of SEQ ID No. 2 and encompass numerous structural variants of residues 28-88 of SEQ ID No. 2. In addition, the specification discloses that Kip1 (28-79) missing 3 amino acids at N-terminal or 15 amino acids at the C-terminal are much weaker as Cdk inhibitors, and deletion of 7 N-terminal amino acids results in no inhibitory activity on Cdk. In view of the much less inhibitory activities of those versions of kip1 (28-79) on Cdk and the unpredictability of protein function from mere amino acid sequence as discussed above, one skilled in the art at the time of the invention would not know how to use the claimed recombinant virus to treat a subject suffering from a hyperproliferative disease or disorder associated with a p27 protein mutation via various administration routes.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.